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13. ABSTRACT *(Maximum 200 words)*

The purpose of the program is to train predoctoral students at Boston University Schools of Medicine and Public Health (BUSM, BUSPH) in research into the etiology, prevention, detection, diagnosis and therapy of breast cancer using the most advanced knowledge and techniques available. In addition to providing training in the student's chosen discipline, the program ensures her or his education in other relevant disciplines. Emphasis is placed on interdisciplinary training in Pathology, Epidemiology, and Cell and Molecular Biology. The goal is that, upon completion of the degree in a particular discipline, trainees will be able to work and communicate effectively with other scientists in interdisciplinary approaches to breast cancer research. This is being accomplished through an interdepartmental curriculum, selection of research supervisors whose research is in breast cancer or highly relevant to breast cancer and participation in monthly seminars. Four trainees, two per year, have been selected on the basis of their GPA, GRE scores, letters of recommendation, interviews, and demonstrated ability in and commitment to research, particularly in breast cancer. All four trainees have completed a summer practical course in mammary carcinogenesis studies in rats; two have completed their first-year courses and are beginning dissertation research or laboratory rotations; they will take the qualifying examination in June, 1996. The two just admitted are beginning course work. In addition to support from this grant, trainees are supported by tuition and stipend given by BUSM and BUSPH.

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FOREWORD

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Marion E. Rogers, MD 10/17/95

PI - Signature Date

NA Not applicable

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b) BCRTG Summer Practical Course, 1995
c) Symposium: HRT and Health
d) First two 1995-96 Seminars

BREAST CANCER RESEARCH TRAINING PROGRAM (BCRTP)

5. INTRODUCTION

Information about breast cancer is increasing rapidly from many sources, but much of it is inconsistent and controversial because of the complexity of the disease and its causes. Difficulties arise also in integration of knowledge and understanding and in extrapolating results between and within scientific disciplines The Program in Research on Women's Health at Boston University Medical Center (BUMC) has been developed to address some of these problems by serving as an integrating and promoting force for research in women's diseases with a major effort focused in breast cancer research. Through the research and teaching collaborative efforts already in place and with the stimulus of this Training Program the work of investigators at BUMC is being brought to bear on training students to conduct research on breast cancer.

The **PURPOSE** of the Program is to: 1) establish a formal multidisciplinary research and academic training program in breast cancer biology and epidemiology; 2) produce graduates in one discipline (Pathology, Epidemiology, Microbiology) who have an understanding of the other disciplines and who can perform collaborative, multidisciplinary research in the etiology, prevention and therapy of the disease; 3) provide training in cell and molecular biology, experimental pathology, carcinogenesis, epidemiology and biostatistics, immunology, toxicology, and nutrition that will permit trainees to explore: a) basic breast cancer cell processes and interactions, including oncogene regulation, cell signalling, and genetic considerations in design of therapeutic agents; b) questions about etiology, prevention and therapy of breast cancer in laboratory animals and human populations; and c) the integration of knowledge derived from the different approaches; 4) maintain and increase collaborative research in breast cancer and closely related areas among faculty and trainees; 5) provide attractive opportunities for all students and, specifically, for women and underrepresented minorities to pursue careers in breast cancer research. We are promoting the development of young investigators who will have a broad, multidisciplinary background in breast cancer biology and epidemiology and intensive training in a specialized research area and who can perform significant research using advanced concepts and techniques and communicate research accomplishments effectively. They will be a resource to meet future personnel requirements for breast cancer research.

The **METHODS** are as follows. Doctoral students committed to cancer research with an interest in breast cancer research are admitted to the Departments of Pathology and Laboratory Medicine, Epidemiology or Microbiology and follow a curriculum specifically designed for this Training Program. BCRTP ensures that each predoctoral student: 1) participates in an appropriate, integrated curriculum focused on breast cancer; 2) has an advisory committee, composed of basic science and epidemiology faculty members with expertise in or closely related to breast cancer research; 3) participates actively in seminars, and local, regional and national meetings in addition to informal research meetings at the school.

The students are closely integrated into the Breast Cancer Working Group in the Program in Research on Women's Health. The Group comprises over 50 members in multidisciplinary teams collaborating in breast cancer ;research and developing new research strategies. The Group stimulates research interactions by providing teaching and discussion of clinical and research topics at monthly meetings. The BCRTP is significantly extending and supplementing the doctoral programs in the participating departments. The BCRTP is directed by Adrianne E. Rogers, MD, and Theodore Colton, DSc, with extensive input from Gail Sonenshein , PhD, and Marianne Prout, MD, who direct the Research on Women's Health Program.

Drs. Rogers and Colton meet at least twice each term and take responsibility for all decisions on student admission, performance and training with substantial input from the faculty Trainers and from the Trainees themselves. Because of the relatively small size of the Program and the extensive interactions with faculty in the Women's Health Program, the Admissions and Performance, Recruitment and Seminar Committees proposed have not been needed and, therefore, have not been formally set up.

Two trainees the first year and now four trainees are supported annually by the BCRTP and BUSM and BUSPH. The two schools have supplemented the BCRTG so that each student receives a stipend of $14,000 per year and tuition for 20-24 credits per year as needed. They have been admitted to the Program via the Pathology and Laboratory Medicine or the Biostatistics and Epidemiology Departments. In the beginning of each academic year all new and returning trainees have met with Drs. Rogers and Colton to review the Program and its requirements and opportunities, and to answer questions and plan each student's curriculum. Trainees are encouraged to consult any of the participating faculty for general advice or further discussion of their research interests, and are directed to appropriate faculty by Drs. Rogers and Colton. Trainees have additional contact with faculty members in courses and seminars.

Drs. Rogers and Colton have met also with each trainee at the end of each semester to discuss trainees' academic performance, to obtain feedback about the program and to advise the trainee on choice of courses and lab rotations. When the students move into their dissertation research, their Faculty Trainer will become their major adviser, but Drs. Rogers and Colton will continue to meet individually with them at least once a year. After passing qualifying exams, trainees' research progress will be reviewed on a regular basis by their dissertation committees, composed of three members from the home department Training Faculty and one member each from the other two departments' Training Faculty. Under appropriate circumstances (need for a particular expertise), one of the committee positions may be filled by non-Trainer faculty from inside or outside BUMC. These committees will meet with the trainee at least twice a year, usually starting within six months of the qualifying exam when the student presents her or his thesis research proposal. Finally, the thesis committee will serve as the examining committee for the thesis defense.

6. **BODY**

The four students are:

1994: Yvette Cozier (BA, Liberal Arts, Harvard Extension School, 1987; MPH, BUSPH, 1994) was admitted to the Biostatistics and Epidemiology DSc. program. She had extensive laboratory experience in Hematology and in Microbiology (1982-1994), strong letters from

faculty and a 3.5 GPA at BUSPH. She was particulary interested in Dr. Rosenberg's epidemiological studies in breast cancer and other diseases in black women, and has subsequently joind Dr. Rosenberg's group for her dissertation research. She is currently taking the Basic and Experimental Pathology course, completing her SPH course requirements and plans to take the qualifying exmaination in summer, 1996. Yvette is an African-American.

Laurie Hafer (BS, Microbiology, Penn. State Univ., 1989) was admitted to the Pathology and Laboratory Medicine Program. She had extensive clinical and research experience in the Immunohistochemistry laboratory at the College of Medicine-University Hospital, Hershey, PA, where she was in charge of research and development with a major focus on breast cancer studies. She had very strong letters from faculty who had supervised and worked with her. She entered intending to pursue interests in immunology and breast cancer but is now more interested in receptor molecular biology and is planning lab rotations in that area. She worked extensively with Drs. Rogers and Delas Morenas the past year in histological and immunohistochemical studies of rat mammary tumors and is working on image analysis of ER & PCNA in them. She has completed many of the course requirements for Pathology and one of the two Epidemiology courses, is currently taking Basic & Experimental Pathology and the Grant-Writing course (see below) in which she is preparing an application to the Mass. Breast Cancer Research Program. She plans to take the qualifying examination in June, 1996.

1995. Sylvia Marecki (BS, Microbiology, Univ. N.H., 1995) was admitted by the Pathology and Laboratory Medicine PhD Program and is in the immunology track. She had significant undergraduate research experience and was awarded two competitive research grants in addition to a four-year scholarship. She had very strong letters from her research adviser and other faculty. As we discussed research opportunities in Immunology, her interests shifted to cancer research from her initial focus on bacteriology, which was the subject of her undergraduate research. Dr. Beller, who directs the Immunology Training Program, discussed with her his interests in cellular immunological responses to breast cancer, and she decided to write a grant application in this area for the Grant-Writing Course (see below) under his direction. Sylvia did an excellent job in her first lab rotation with Dr. Rogers in the rat DMBA carcinogenesis study, participated in the practical course (see below) and is well-oriented to breast cancer research.

Paul Mange (BS Biology, Yale, 1988) was admitted to the Biostatistics and Epidemiology PhD program. This program differs from the DSc program in the SPH in being a more extensive joint program with the Mathematics Dept. on the Charles River Campus of BU and in requiring a more sophisticated mathematics and biostatistics curriculum and dissertation. After completing 1 1/2 years of medical school at Univ. Mass, Paul left to pursue interests in math and statistics and worked in biomedical applications of these areas as Sr. Research Analyst in Psychiatric Epidemiology at the Mass. General Hospital. He had excellent letters from faculty and colleagues. He completed the practical course (see below) and contributed valuable statistical questions and insights to the student-faculty discussions in that course. He is taking the Basic and Experimental Pathology course and other courses required for his program.

In the summer of 1995 one continuing and one entering student (Hafer, Marecki) participated in an intensive grant-writing workshop which is continuing as a course this fall term. Through that course they have met with faculty and begun preliminary development of their own research projects.

All four BCRTP students participated actively in the month of August in the practical course in the setting up of a new DMBA mammary tumorigenesis study under Dr. Rogers' direction. They learned basic methods for such studies, participated in feeding, weighing and observing the animals and in performing pair-feeding and fluid intake measurements. Three members of the Pathology faculty and staff introduced them to clinical studies of breast cancer. Dr. De las Morenas taught them basics of breast cancer pathology; Dr. Burke taught them basics of image analysis focused on estrogen receptor assay; Dr. Yang and one of the students, Laurie Hafer, taught them basics of immunohistochemistry staining and interpretation. Dr. Rogers taught them basics of the histopathology of rat mammary gland tumors and discussed recent research papers from other laboratories with them.

The two students who entered in 1994 participated in the seminar series and in Breast Cancer Working Group meetings in addition to a variety of other seminars in the two schools. This year we started off with a seminar by Dr. Craig Jordan, Director of Breast Cancer Research at Northwestern. The students had a 1 1/2 hour luncheon and discussion with him before the seminar.

7. CONCLUSIONS

The Program is actively recruiting, attracting and retaining excellent students from diverse backgrounds to focus on breast cancer research. The four students are a cohesive group who study and work together well. They interact extensively with Drs. Rogers & Colton and with other students and faculty working in breast cancer research and working in clinical settings with breast cancer. They are doing well in course work and in initial laboratory work. The interdisciplinary focus in strong, fostered by the summer practical course, the required epidemiology and pathology courses, seminars, and frequent formal and informal meetings of the students with Drs. Rogers and Colton. The students are progressing as expected (or more rapidly than expected) through their course work and into research, a commendable result.

9. APPENDIX

BREAST CANCER WORKING GROUP SEMINARS

June 14, 1995	Robert Cardiff, MD Chief, Medical Pathology UC Davis	"The Amazing World of Transgenic Mice and Human Breast Cancer"
May 11, 1995	Francine Foss, MD Assist. Professor Univ. Hospital	"Modulation of Drug Resistance in Breast Cancer Cell Lines"
April 28, 1995	Abdul Traish, PhD Assoc. Prof., Dept. of Biochemistry	"Diagnostic Potential of ER Epitopes"
March 23, 1995	Carol Rosenberg, MD Assist. Professor Boston City Hospital	"Genetic Alterations in Pre-Malignant Breast Disease"
Jan. 12, 1995	Ted Colton, ScD Professor, BU Sch. of Public Health	"Epidemiologic Analysis of Breast Implants"
Dec. 8, 1994	Ann Ashengrau, ScD, MS Assoc. Prof., BU SPH; Julie Palmer, ScD, Assoc. Prof.,Slone Epi. Unit; Yuging Zhang, ScD, Assist. Prof., BU SPH	"Epidemiology of Studies on Breast Cancer"
Nov. 28, 1994	Maureen Kavanah, MD Assoc. Prof., BU Hospital	"Obtaining Breast Cancer Tissue"
Oct. 20, 1994	Sanwat Hussain, MD Assoc. Prof., Radiology Chief, General Radiology	"Breast Imaging"

SEMINARS HELD IN COLLABORATION

May 4, 1995	Nancy Davidson, MD, Johns Hopkins Univ.	"Programed Cell Death"

(Given in collaboration with the Mass. Dept. of Public Health Breast Cancer Research Lecture Series)

Breast Cancer: Experimental Pathology
Breast Cancer Research Training Grant Summer Practical Course
August 21-September 2, 1995

Conferences

Monday, August 21, 11:00
Ongoing Mammary Carcinogenesis Studies in Rats: Methods, results, statistical evaluation
Dr. Rogers, Yvette Iskander

Tuesday, August 22, 11:00
Breast Cancer Pathology
Dr. De las Morenas

Wednesday, August 23, 11:00
Discussion of assigned paper (Cancer Res 55:3483, '95)
Dr. Rogers

Thursday, August 24, 11:00
Image analysis: Hormone Receptors in Breast Cancer.
Dr. Burke

Tuesday, August 29, 11:00
Breast Cancer Pathology
Dr. De las Morenas

1:00 Immunohistochemistry: Theory, methods & results
Dr. Yang, Laurie Hafer

Practical exercises

Students will participate in the following daily exercises:

Feed, weigh, inspect the rats in the current study of mammary carcinogenesis.

Measure tea, water and feed intake of rats in the current study.

Stain and examine 1 IHC preparations.

Examine H & E slides of mammary tumors and normal glands from rats.

Review and evaluate data from the study of mammary carcinogenesis just completed.

The method for intragastric administration of carcinogen will be demonstrated by Yvette Iskander.

Adrianne E. Rogers, M.D.
014-30-2797

Program in Research on Women's Health
Interdisciplinary Seminar Series
Current Directions in Research on Women's Health
Boston University Medical Center
May 17, 1995

HORMONE REPLACEMENT THERAPY AND HEALTH: ISSUES IN 1995

Abstract:

ROLE OF HORMONE REPLACEMENT THERAPY IN THE PREVENTION AND TREATMENT OF OSTEOPOROSIS. M.F. Holick Vitamin D, Skin, and Bone Research Laboratory, Endocrinology Section, Department of Medicine, Boston University Medical Center, Boston, MA.

It is well recognized that estrogen plays an important role in maintaining good skeletal health. The bone forming cells, osteoblasts, have receptors for estrogen and respond to this hormone. Although the exact mechanism by which the lack of estrogen increases the mobilization of calcium from the skeleton is not fully elucidated, there is mounting evidence that during menopause, there is an increase in the production of interleukin-6 which, in turn, is a potent stimulator of osteoclastic activity. With the onset of menopause as defined by decreased serum levels of estradiol and increased levels of follicle stimulation hormone, luteinizing hormone results in a 1 to 3% decrease bone density/yr. When hormone replacement therapy is instituted, this relatively rapid bone loss is substantially diminished. Originally, it was thought that only during the first 10 years after menopause women would benefit from hormone replacement therapy for their skeleton. However, there is mounting evidence that women can benefit from the bone protecting effect of estrogen whether they are 10 years or 30 years after menopause. The two approaches for hormone replacement therapy include either cyclical therapy with estrogen and a progestin, or, alternatively, to provide estrogen with low dose progestin. There remains concern about the potential role of hormone replacement therapy on increasing the risk of breast cancer. A multitude of studies have been conducted some of which have shown a small increased risk while others have shown no substantial risks. Overall, when not contraindicated, estrogen therapy is of great value in the protection of the skeleton for women who are menopausal.

Adrianne E. Rogers, M.D.
014-30-2797

Hormone replacement therapy and breast cancer: Issues in 1995
M. N. Prout, 5/17/95

Associations between HRT and breast cancer have been explored in case-control and cohort studies. 39 studies of ERT show relative risks (RR) for ever use of 1.0, for long-term use of 1.3; in European studies RRs are up to 2.0. RRs for EPRT from 6 studies are 1.4 in Europe vs. 1.2 in the U.S.; for use >6 years, 4 vs. 1.6. RRs vary by type of estrogens and progestins used: premarin and provera in the US, estradiol and "testosterone-like" progestins in Europe. Some studies show higher risk with higher dose, longer duration, and current use. Calculations and comparisons of dose vary and separating the effects of ERT, PRT, and EPRT are difficult.

Decreased breast cancer mortality in HRT users is reported in case-control and cohort studies. Biases due to selection of healthy drug users and increased surveillance have been tested. Increased RR (1.4) for in situ but not invasive breast cancer was reported by Schairer in women who had mammograms.

HRT use by women at high risk for breast cancer remains controversial. For women with a prior diagnosis of breast cancer, data is limited to small case series; nonetheless DiSaia has suggested that HRT be considered in these women. In the BCDDP followup cohort, 18% of women with breast cancer in a first degree relative and women who had breast biopsies had the same increased risk of in situ breast cancer as the entire cohort. Studies of HRT in women with atypical hyperplasia and hyperplasia are limited by the low prevalence, inconsistent diagnoses, and uncertain prognoses of these histologies.

Epidemiologic and laboratory studies support an association of breast cancer risk with cumulative lifetime exposure to "hormones". Quantifying effects of HRT compared to all other endogenous and exogenous hormone exposures remains controversial.

HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR DISEASE: UPDATE 1995. Lynn Rosenberg, Slone Epidemiology Unit, School of Public Health, Boston University School of Medicine.

Observational studies suggest that estrogen replacement therapy (ERT) reduces the risk of coronary artery disease, that the benefit disappears after cessation of use, and that it has been overestimated because of the greater tendency of women at lower risk to use ERT. A recent study shows that users stop taking estrogen when they develop symptoms of serious illness, which results in overestimation of the benefit of ERT in current users. Insufficient data exist to document an effect of HRT (estrogen together with a progestin) on risk.

Recent data from the PEPI trial, a randomized trial of ERT, HRT, and placebo, indicate that all the drug regimens increased HDL relative to placebo. The increase was greatest for estrogen alone (5.6 mg/dL) and least for estrogen with Provera (about 1.4 mg/dL); estrogen with micronized progesterone increased HDL by 4.1mg/dL. Adenomatous or atypical endometrial hyperplasia developed in 34% of women with a uterus taking ERT versus 1% of the placebo group; 6% of ERT users had hysterectomies versus 1% of the placebo group.

The recent data indicate that the cardiovascular benefit of current ERT use has been overestimated, that ERT alone has excellent effects on HDL but is problematic for use by women with a uterus, and that the most widely used HRT regimen, estrogen with Provera, has a marginal beneficial effect on HDL.

Women considering the use of ERT or HRT need to weigh the potential reduced risks of cardiovascular disease and osteoporotic fractures against the potential increased risks of breast and endometrial cancers in light of their own risk factors and the alternatives. This consideration should include the ages at which the putative risks and benefits occur, and whether they are transient or long-lasting.

Abstract. Hormone Replacement Therapy (HRT) and Endometrial Cancer (ECA). Samuel Shapiro. Slone Epidemiology Unit, Boston University School of Public Health.

It is well established that the use of unopposed estrogens (mainly Premarin) increases the risk of ECA by about three-fold after about 5 years of use, and by as much as ten-fold after 10+ years. The risk is also dose-related. It declines slowly after discontinuing use, but continues to remain elevated for many years. By contrast, oral contraceptives (estrogens + progestogens) decrease the risk; thus it has been argued that the addition of a progestogen to estrogen (usually Premarin + Depoprovera) should also reduce the risk. Among post-menopausal women, however, combined HRT has not been in use commonly enough or long enough for rigorous assessment. The evidence is preliminary, but it suggests that the analogy with oral contraceptives may be simplistic: there does not appear to be a reduction in the risk of ECA, and for long-term use an increased risk has not been ruled out. In addition, many women prefer estrogens alone because of the side effects of combined therapy (such as bleeding, bloating, weight gain, and mood changes).

Insufficient attention has been paid to the longitudinal effects of HRT. On the average, for women who have not had a hysterectomy and who commence estrogen use at about age 50, the risk of endometrial cancer during the next ten years outweighs any potential benefits. Then, with advancing age the risk continues to increase with each additional year of use. That increase, as well as a possible increased risk of breast cancer, must be weighed against the potential benefits. For women who use combined HRT the information required to do so is not yet available.

BOSTON UNIVERSITY MEDICAL CENTER

Program in Research on Women's Health

Interdisciplinary Seminar Series
Current Directions in Research on Women's Health

Commonwealth of Massachusetts Course on Breast Cancer

Copresents

Craig Jordan, Ph.D., D.Sc.

Director of Breast Cancer Research
Northwestern University Medical School

The Transfection of the ER Gene into Breast Cancer Cells: "The World Turned Upside Down"

Date: Thursday, September 28, 1995

Time: 4:00 to 5:00 p.m., Reception to follow

Place: Atrium C/D Conference Room

BOSTON UNIVERSITY MEDICAL CENTER
CANCER PREVENTION AND CONTROL GRAND ROUNDS
FRIDAY SEPTEMBER 29, 1995, 12:00-1:00 PM
EVANS SEMINAR ROOM, FIRST FLOOR EVANS BUILDING

"CAN TAMOXIFEN PREVENT BREAST CANCER?"

DR. MARIANNE PROUT
ASSOCIATE PROFESSOR OF PUBLIC HEALTH AND SURGERY
BOSTON UNIVERSITY SCHOOL OF MEDICINE/
SCHOOL OF PUBLIC HEALTH

LUNCH WILL BE PROVIDED
NURSING CEU'S AND
PHYSICIAN CME'S PROVIDED

Adrianne E. Rogers, M.D.
014-30-2797